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STATISTICAL ANALYSIS PLAN

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Ocrelizumab—F. Hoffmann-La Roche Ltd
Statistical Analysis Plan BN29739

Clinical Study Report: ocrelizumab - F. Hoffmann-La Roche Ltd
Protocol BN29739 Report Number 1079337

TABLE OF CONTENTS

1.	BACKGROUND	6
2.	STUDY DESIGN	6
2.1	Protocol Synopsis	7
2.2	Outcome Measures	7
2.2.1	Primary Immunization Outcome Measure.....	7
2.2.2	Secondary Outcome Measures	7
2.2.3	Immunophenotyping Outcome Measures	8
2.2.4	Safety Outcome Measures	9
2.3	Determination of Sample Size	9
2.4	Analysis Timing	9
3.	STUDY CONDUCT	9
3.1	Randomization Issues	9
4.	STATISTICAL METHODS	10
4.1	Analysis Populations	10
4.1.1	Intent-to-Treat Population	10
4.1.2	Observed Cases Population	10
4.1.3	Safety Population	10
4.2	Analysis of Study Conduct.....	11
4.3	Analysis of Treatment Group Comparability	11
4.3.1	Demography	12
4.3.2	Multiple Sclerosis Disease History.....	12
4.3.3	Previous and Concomitant Diseases Other than Multiple Sclerosis.....	12
4.3.4	Previous and Concomitant Treatments	13
4.3.5	Passive Immunization History and Vaccination History	13
4.3.6	Expanded Disability Status Scale	14
4.3.7	Pre-Vaccination/Pre-Immunization Immunology Assessments	14
4.3.8	Baseline Magnetic Resonance Imaging Data	15
4.4	Outcome Analysis.....	16

4.4.1	Primary Immunology Endpoint.....	16
4.4.2	Secondary Immunology Endpoints	17
4.4.2.1	Tetanus Toxoid Adsorbed Vaccine Response Measured 4 weeks after Vaccine Administration	17
4.4.2.2	23-Valent Pneumococcal Polysaccharide Vaccine and Pneumococcal Conjugate Booster.....	18
4.4.2.3	Keyhole Limpet Hemocyanin	20
4.4.2.4	Influenza Vaccine Response	20
4.4.3	Other Secondary Endpoints (Magnetic Resonance Imaging)	21
4.4.4	Exploratory Immunology Endpoints	21
4.4.4.1	Overall Antibody Response to 23-PPV Vaccine	21
4.4.4.2	Overall Antibody Response to 13-PCV Vaccine	22
4.4.5	Sensitivity Analyses.....	22
4.4.6	Subgroup Analyses	22
4.5	Immunophenotyping Analyses	22
4.6	Safety Analyses	23
4.6.1	Exposure to Study Medication (Ocrelizumab).....	23
4.6.1.1	Exposure to Ocrelizumab during the ISP	23
4.6.1.2	Exposure to Ocrelizumab during the OOE.....	24
4.6.2	Adverse Events	25
4.6.2.1	Adverse Events during the ISP	25
4.6.2.2	Adverse Events during the OOE.....	27
4.6.2.3	Adverse Events, All Study Periods	27
4.6.3	Selected Adverse Events.....	28
4.6.3.1	Progressive Multifocal Leukoencephalopathy.....	28
4.6.3.2	Infections and Serious Infections	28
4.6.3.3	Infusion-Related Reactions.....	28
4.6.3.4	Malignancies and Premalignant Lesions	30
4.6.4	Laboratory Data	30
4.6.4.1	General Laboratory Evaluation	30
4.6.4.2	Anti-Drug Antibodies.....	31
4.6.5	Vital Signs and Electrocardiogram.....	31
4.6.6	Pregnancies.....	32

4.7	Missing Data.....	32
4.8	Interim Analyses	32

LIST OF APPENDICES

Appendix 1	Protocol Synopsis	33
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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
13-PCV	13-valent pneumococcal conjugate vaccine
23-PPV	23-valent pneumococcal polysaccharide vaccine
ADA	anti-drug antibody
CCOD	clinical cutoff date
eCRF	electronic Case Report Form
EDSS	Expanded Disability Status Scale
ELISA	enzyme-linked immunosorbent assay
Gd	gadolinium
GMT	geometric mean titer
HI	hemagglutination inhibition
IFN- β	interferon beta
Ig	immunoglobulin
IgA	immunoglobulin A
IgG	immunoglobulin G
IgM	immunoglobulin M
IRR	infusion-related reaction
ISP	Immunization Study Period
ITT	Intent-to-Treat
IV	intravenous
KLH	keyhole limpet hemocyanin
LLQ	lower limit of quantification
MRI	magnetic resonance imaging
MS	multiple sclerosis
OC	Observed Cases
OOE	Optional Ocrelizumab Extension
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy
PT	Preferred Term
RMS	relapsing forms of multiple sclerosis
SAP	Statistical Analysis Plan
SC	subcutaneous
SFU	Safety Follow-Up
SOC	System Organ Class
SPMS	secondary progressive multiple sclerosis
TB	tuberculosis
TT	tetanus toxoid

Ocrelizumab—F. Hoffmann-La Roche Ltd
5/Statistical Analysis Plan BN29739

Clinical Study Report: ocrelizumab - F. Hoffmann-La Roche Ltd
Protocol BN29739 Report Number 1079337

1. **BACKGROUND**

This Phase IIIb, multicenter, randomized, open-label study is designed to evaluate immune response to vaccines in patients with relapsing forms of multiple sclerosis (MS) after administration of a dose of ocrelizumab.

The clinical cutoff date (CCOD) will be the earliest date on which all randomized patients will have completed the Week 24 visit for Group A, completed the Week 12 visit for Group B, or prematurely discontinued during the Immunization Study Period (ISP) if they have discontinued before the Week 24 visit for Group A or before the Week 12 visit for Group B.

The scope of this statistical analysis plan includes the following:

- The primary analysis of immunology and safety endpoints evaluated in the ISP
- Analysis of all data available at the CCOD from the following periods:
 - The Optional Ocrelizumab Extension (OOE) after completing the ISP
 - The Safety Follow-Up (SFU) Period after the ISP for patients who did not enter the OOE
 - The SFU Period after completing the OOE

2. **STUDY DESIGN**

This Phase IIIb, multicenter, randomized, open-label study is designed to evaluate immune response to vaccines after administration of a dose of ocrelizumab.

The study consists of the following periods: Screening, an ISP, an OOE, SFU, and a Continued B-cell Monitoring Period.

Following screening, approximately 100 adult patients will be randomized into Groups A and B (2:1 active:control) to compare responses to immunization. Patients in Group B are to receive immunization with tetanus toxoid (TT)-containing adsorbed vaccine, 23-valent pneumococcal polysaccharide vaccine (23-PPV), influenza vaccine, and repeated administration with keyhole limpet hemocyanin (KLH). Group B patients will not receive ocrelizumab, but will remain treatment-naïve or continue with interferon beta (IFN- β) treatment until optional ocrelizumab treatment at the end of the ISP.

Patients in Group A are to first receive a 600 mg dose of ocrelizumab, 300mg on Day 1 (Infusion 1) and 300mg on Day 15 (Infusion 2), and starting 12 weeks after Day 1 (Infusion 1 of ocrelizumab) are to receive a similar immunization course to Group B. Group A will be further subdivided into two groups (non-randomly, based on seasonality considerations) to evaluate the effectiveness of a booster 13-valent pneumococcal conjugate vaccination (13-PCV; Group A1) or influenza vaccination (Group A2). For additional details, see the protocol and Schedule of Assessments.

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in [Appendix 1](#). Please note that, in the event that the version of the protocol synopsis in [Appendix 1](#) differs from the version in the current protocol, then the version in the current protocol takes precedence over the version included in this Statistical Analysis Plan (SAP). [Appendix 1](#) will only be updated in the event that the protocol synopsis amended in the future and includes changes that impact this SAP.

2.2 OUTCOME MEASURES

2.2.1 Primary Immunization Outcome Measure

The primary outcome measure is the proportion of patients in Groups A (i.e., combined Groups A1 and A2) and B with a positive response (IgG) to TT vaccine measured 8 weeks after TT vaccine administration (defined fully in Section [4.4.1](#)).

2.2.2 Secondary Outcome Measures

The secondary outcome measures are as follows:

- TT response

The proportion of patients in Groups A (A1 and A2 combined) and B with a positive response (IgG) to TT vaccine measured 4 weeks after booster TT vaccine administration (defined fully in Section [4.4.2.1](#))

Mean levels of anti-tetanus antibody in patients in Groups A (A1 and A2 combined) and B measured immediately prior to and 4 weeks after a booster TT vaccine

- 23-valent pneumococcal polysaccharide vaccine (23-PPV) response and 13-PCV booster response:

The proportion of patients in Groups A1, A2, A (A1 and A2 combined), and B with positive responses against an individual anti-pneumococcal antibody serotype measured 4 weeks after the 23-PPV (23 serotypes) (defined fully in Section [4.4.2.2](#))

The proportion of patients in Groups A1, A2, A (A1 and A2 combined), and B with a positive response against at least 2 out of the 23 serotypes measured 4 weeks after and 8 weeks after administration of the 23-PPV vaccine (defined fully in Section [4.4.2.2](#))

The proportion of patients in Groups A1, A2, A (A1 and A2 combined), and B with positive responses against at least 50% of the serotypes (≥ 12 of 23) measured 4 weeks after administration of the 23-PPV vaccine (defined fully in Section [4.4.2.2](#))

The proportion of patients in Groups A1, A2, A (A1 and A2 combined), and B with positive responses against each of the 23 serotypes measured 8 weeks after patients received the 23-PPV vaccine (which is 4 weeks after Group A1 received the booster 13-PCV) (defined fully in Section [4.4.2.2](#))

Mean levels of anti-pneumococcal antibody (23 serotypes) in patients in Groups A1, A2, A (A1 and A2 combined), and B measured immediately prior to, 4 weeks after and 8 weeks after patients received the 23-PPV (this is 4 weeks after Group A1 received the 13-PCV immunization)

- KLH

Mean levels of anti-KLH antibody (IgG) in patients in Groups A (A1 and A2 combined) and B measured immediately prior to the first administration of KLH and 4 weeks after the last administration of KLH

Mean levels of anti-KLH antibodies (IgG and IgM) in Groups A (A1 and A2 combined) over time at 4, 8, and 12 weeks after first KLH immunization

- Influenza vaccine response:

Proportion of patients in Groups A2 and B who achieve seroprotection defined as specific hemagglutination inhibition (HI) titers >40 at 4 weeks post-immunization

Proportion of patients in Groups A2 and B who achieve a 2-fold increase in specific HI titers at 4 weeks post-immunization

Proportion of patients in Groups A2 and B who achieve a 4-fold increase in specific HI titers at 4 weeks post-immunization

Proportion of patients in Groups A2 and B with seroconversion (i.e., a pre-vaccination antibody titer <10 and a post-vaccination HI titer >40)

Strain-specific geometric mean titers (GMTs) in patients in Groups A2 and B at baseline and Week 4

Strain-specific GMT ratio (post-vaccination:pre-vaccination) in patients in Groups A2 and B

- Magnetic resonance imaging (MRI) assessments in patients in Groups A (A1 and A2 combined) and B to evaluate the long-term effects of ocrelizumab on MRI parameters of disease activity and progression during the OOE

2.2.3 Immunophenotyping Outcome Measures

The humoral and cellular immunity outcome measures in this study are as follows:

- Flow cytometry panel (i.e., circulating B cells and T cells), which will include (but is not limited to) the following cells:

Total B cells (CD19+)

B-cell subsets (e.g., memory B cells, naïve B cells, and plasma cells)

Total T cells (CD3+)

T helper cells (CD3+ and CD4+)

Cytotoxic lymphocyte T (CD3+and CD8+)

Natural killer cells (CD3– and CD16/56+)

- Quantitative Ig: Ig levels (including total Ig, IgG, IgG subtypes, IgM, and IgA)

Ocrelizumab—F. Hoffmann-La Roche Ltd

8/Statistical Analysis Plan BN29739

Clinical Study Report: ocrelizumab - F. Hoffmann-La Roche Ltd

Protocol BN29739 Report Number 1079337

2128

2.2.4 Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Vital signs pre-, during, and post-infusion
- Hematologic laboratory tests
- Anti-drug antibody (ADA) formation
- Urinalyses
- Incidence and severity of adverse events associated with ocrelizumab and study immunizations

2.3 DETERMINATION OF SAMPLE SIZE

For the positive response to TT-containing adsorbed vaccine measured 8 weeks after the administration of vaccine, if both the control and active (ocrelizumab) groups have 70% response rates, the expected half-width of the resulting 95% CI of the difference of 2 response rates is 0.201. To achieve this precision, approximately 100 patients will be enrolled using a 2:1 randomization ratio into active ocrelizumab (Group A) and control (Group B) groups.

2.4 ANALYSIS TIMING

The primary analysis of immunology and safety endpoints evaluated in the ISP and the analysis of available OOE data will be performed at the CCOD, which is defined as the date when all randomized patients have completed the Week 24 visit for Group A or the Week 12 visit for Group B, or the date on when all randomized patients have prematurely discontinued the ISP if they have discontinued before the Week 24 visit for Group A or before the Week 12 visit for Group B.

Regular interim safety analyses may be performed, approximately every 6 months, to allow pooled safety analyses of MS patients treated with ocrelizumab. These analyses are not described in this document.

Interim pharmacokinetic (PK) analyses may also be performed during the study. These PK analyses are not described here but in a separate document.

3. STUDY CONDUCT

3.1 RANDOMIZATION ISSUES

Patients were randomized into two groups (Group A or Group B) in a 2:1 randomization ratio. Randomization was performed by an independent vendor via an interactive response system.

4. STATISTICAL METHODS

Except where stated otherwise, all tabular and graphical summaries of data, which are presented by treatment group, will separately show results from the following four groups:

- Group A1 (ocrelizumab + 13-PCV vaccine)
- Group A2 (ocrelizumab + influenza vaccine)
- Group A overall (Groups A1 + A2)
- Group B (control)

All listings will show study data for each treatment group in the order shown above.

4.1 ANALYSIS POPULATIONS

4.1.1 Intent-to-Treat Population

All randomized patients will be included in the Intent-to-Treat (ITT) Population. Patients who prematurely withdraw from the study for any reason and for whom an assessment is not performed for whatever reason will still be included in the ITT analysis. Patients who receive an incorrect medication or vaccination rather than the one they are assigned to will be summarized according to their randomized treatment group.

In the event that at least 1 randomized patient withdraws from the study before the end of the ISP, then tabular summaries of baseline characteristics only will be presented for the ITT Population. If all randomized patients complete the ISP, then no summaries/analyses will be presented for ITT Population.

4.1.2 Observed Cases Population

The Observed Cases (OC) Population is defined as all randomized patients who complete the ISP. Patients who receive an incorrect medication or vaccination rather than the one that they are assigned to will be summarized according to their randomized treatment group.

All immunization outcome measures will be analyzed using the OC Population.

4.1.3 Safety Population

The Safety Population will include all patients who received any ocrelizumab or any vaccine. Randomized patients who received an incorrect medication or vaccine rather than the one they were assigned to will be summarized in the group according to the medication or vaccine actually received.

All safety outcome measures will be analyzed using the Safety Population.

4.2 ANALYSIS OF STUDY CONDUCT

All data up to the point of the CCOD will be included to evaluate study conduct. This will include complete data from the ISP and any data from the OOE and SFU Periods available at the CCOD.

The following analyses will be performed to evaluate the study conduct:

- Summary of enrollment by country and center (numbers and percentages of patients enrolled, presented by treatment group)
 - Summaries of randomized patients, of the ITT Population if any summaries are produced for this population, and of the OC and Safety Populations (numbers and percentages of patients in each population, presented by treatment group)
- Summary of patient disposition for the ISP and OOE and SFU Periods (at each visit/during each study period, numbers and percentages of patients completing, discontinuing and ongoing, presented by treatment group)
- Summary of reasons for patients discontinuing during the following study periods (numbers and percentages of patients discontinuing for each reason within each period, presented by treatment group):

ISP

SFU Period after the ISP (these patients did not enter the OOE)

OOE

SFU Period after completing the OOE

Study as a whole

A listing of reasons for all patient discontinuations from the study will also be provided.

- Listing of key eligibility criteria violations and other major protocol deviations

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

For continuous variables, the mean, median, SD, minimum and maximum will be presented for each treatment group. For categorical variables, number and percentage of patients in each category will be presented for each treatment group.

Except where stated, all assessments of treatment group comparability will utilize the date of the baseline visit (not the date of the screening visit) as the reference point in time.

Except where stated, summary tables will be presented for both OC and Safety Populations. In the event that at least one randomized patient withdraws from the study before the end of the ISP, then tabular summaries of baseline characteristics will also be presented for the ITT Population.

4.3.1 Demography

The following demographic characteristics will be analyzed:

- Age (years): summary statistics, including mean, median, SD, minimum and maximum, percentage, and number in each age (at randomization) category (age categories < 18, 18–65, > 65, used in the Development Safety Update Report)
- Sex: number and percentage of male and female patients
- Race: number and percentage of patients who are White, Black or African American, Asian (Indian Subcontinent, Other than Indian subcontinent), American Indian or Alaskan native, Native Hawaiian or other Pacific Islander, and Other
- Ethnicity: number and percentage of patients who are Hispanic or Latino and not Hispanic or Latino
- Weight (kg): summary statistics, including mean, median, SD, minimum, and maximum
- Body mass index (calculated from weight and height): summary statistics, including mean, median, SD, minimum, and maximum

Listings will be provided for demography and for randomization information.

4.3.2 Multiple Sclerosis Disease History

The following MS disease history characteristics will be analyzed:

- Duration since MS-symptom onset (years; i.e., divided by 365.25): summary statistics, including mean, median, SD, minimum, and maximum
- Duration since MS diagnosis (years; i.e., divided by 365.25): summary statistics calculated, including mean, median, SD, minimum, and maximum

Duration since MS symptom/diagnosis onset will be calculated up to the randomization date. If the month of symptom/diagnosis onset date is missing, the month of January will be used. If the day of symptom/diagnosis onset date is missing, the first of the month will be used.

- Type of MS diagnosed: number and percentage of patients with relapsing MS, secondary progressive MS with relapses (SPMS with relapses), secondary progressive MS without relapses (SPMS without relapses), progressive relapsing MS, and primary progressive MS

A listing of MS disease history will also be provided.

4.3.3 Previous and Concomitant Diseases Other than Multiple Sclerosis

The following previous and concomitant diseases other than MS will be analyzed:

- Previous diseases (other than MS) by System Organ Class (SOC) and Preferred Term (PT): number and percentage of patients with previous non-MS diseases, and number and percentage of patients with a history of each disease

- Concomitant diseases (other than MS) by SOC and PT: number and percentage of patients with concomitant non-MS diseases, and number and percentage of patients with each disease

A glossary listing of SOC terms, PTs, and verbatim terms for all diseases will also be provided.

4.3.4 Previous and Concomitant Treatments

Summaries of previous and concomitant treatments will be presented for the Safety Population only. The number of treatments and number and percentages of patients receiving treatments will be presented.

Treatments for MS

The following treatments for MS will be summarized:

- Previous treatments for MS by superclass term and PT
- IFN- β concomitant treatment allowed for MS during the ISP for patients in Group B
- Concomitant treatments for MS starting during the SFU Period following the ISP by PT for patients who did not enter the OOE
- Concomitant treatments for MS starting during the SFU Period following the OOE by PT

A listing of previous MS treatments by PT will be presented.

Other Treatments

The following other treatments will be analyzed:

- Previous treatments by superclass term and PT
- Previous procedures/surgeries by superclass term and PT
- Concomitant treatment present at baseline by superclass term and PT
- Procedures/surgeries present at baseline by superclass term and PT

A glossary listing of superclass terms, PTs, and verbatim terms for all medications and procedures will be provided. A glossary listing of grouping (procedures category), superclass terms, and PTs will also be provided.

4.3.5 Passive Immunization History and Vaccination History

The following information on passive immunization history and vaccination history will be analyzed:

- Passive immunization history: number and percentage of patients (yes or no) who have received the following passive immunizations: tetanus immunoglobulin, hepatitis B immunoglobulin, hepatitis A immunoglobulin, rabies antiserum, varicella zoster immunoglobulin, and other

- Vaccination history: number and percentage of patients (yes or no) who have received the following vaccinations: tetanus, pneumococcus polysaccharide, pneumococcal booster, diphtheria, influenza, KLH, varicella, measles, mumps, rubella, hepatitis B, hepatitis A, bacillus Calmette-Guerin, polio, pertussis, haemophilus influenza B, meningococcal, typhoid, yellow fever, smallpox, rotavirus, human papilloma virus, herpes zoster, and other. For tetanus, the number of years since prior tetanus vaccination will be summarized (summary statistics: mean, median, SD, minimum, and maximum).

Listings of passive immunization history and vaccination history will also be provided.

4.3.6 Expanded Disability Status Scale

The following characteristics of baseline Expanded Disability Status Scale (EDSS) (pre-dose) will be analyzed:

- Number and percentage of patients in each EDSS category (<4.0, and ≥4.0)
- Summary statistics, including mean, median, SD, minimum, and maximum

A listing of all EDSS assessments made during the whole study will be provided. Since an EDSS assessment should be performed if progressive multifocal leukoencephalopathy (PML) is suspected, this listing will include all available EDSS assessments, i.e., baseline and postbaseline.

4.3.7 Pre-Vaccination/Pre-Immunization Immunology Assessments

For the OC Population, the following pre-vaccination/pre-immunization immunology assessments will be summarized descriptively (note that, by design, some of these pre-vaccination/pre-immunization assessments are taken after baseline [Day 1]):

- Levels of anti-tetanus antibodies in patients measured prior to booster TT vaccine administration (prior to the start of ocrelizumab treatment)
- Levels of anti-pneumococcal antibody (µg/mL) against each of the 23 different serotypes (see Section 4.4.2.2) measured prior to administration of the 23-PPV vaccine
- Levels of anti-pneumococcal antibody (µg/mL) against each of the 23 different serotypes (see Section 4.4.2.2) measured 4 weeks after administration of the 23-PPV vaccine (which, for Group A1 patients, is prior to administration of the 13-PCV booster vaccine)
- Levels of anti-KLH antibody IgG measured immediately prior to first KLH administration (prior to the start of ocrelizumab treatment)
- In Groups A2 and B only, strain-specific GMTs measured immediately prior to immunization with the influenza vaccine (which can occur prior to or after the start of ocrelizumab treatment)

Each assessment listed above will be summarized descriptively by treatment group (as individually specified for each assessment) for the following summary statistics:

- Number and percentage of patients with values \leq lower limit of quantification (LLQ)
- Number and percentage of patients with values $>$ LLQ
- Geometric mean of known values $>$ LLQ
- 95% CI for geometric mean of known values $>$ LLQ, calculated using a normal approximation method on the log scale and then back-transformed to the original scale
- Geometric mean of all nonmissing values, imputing $\text{LLQ} \div 2$ for values \leq LLQ
- 95% CI for geometric mean of all nonmissing values, imputing $\text{LLQ} \div 2$ for values \leq LLQ, calculated using a normal approximation method on the log scale and then back-transformed to the original scale
- Median of known values $>$ LLQ
- Median of all nonmissing values, imputing $\text{LLQ} \div 2$ for values \leq LLQ

Pre-vaccination/pre-immunization assessments for the following exploratory immunology endpoints may be summarized descriptively using the same statistics listed above, depending on data availability at the time of the primary analysis:

- Overall levels of antibodies to the 23-PPV vaccine, i.e., IgG (using ELISA), measured prior to administration of the 23-PPV
- Overall levels of antibodies to the 23-PPV vaccine, i.e., IgM (using ELISA), measured prior to administration of the 23-PPV vaccine
- Levels of overall antibody response to the 13-PCV vaccine, i.e., IgG (using ELISA), measured 4 weeks after administration of the 23-PPV vaccine (which, for Group A1 patients, is prior to administration of the 13-PCV booster vaccine)
- Levels of overall antibody response to the 13-PCV vaccine, i.e., IgM (using ELISA), measured 4 weeks after administration of the 23-PPV vaccine (which, for Group A1 patients, is prior to administration of the 13-PCV booster vaccine)

4.3.8 Baseline Magnetic Resonance Imaging Data

The following characteristics of baseline MRI data will be analyzed:

- Volume of T2 lesions at baseline: summary statistics, including mean, median, SD, minimum, and maximum
- Number of T2 lesions at baseline: summary statistics, including mean, median, SD, minimum and maximum, and number and percentage of patients in each category (0–5, 6–9, and $>$ 9 T2 lesions at baseline)
- Number of gadolinium (Gd)-enhancing T1 lesions at baseline: summary statistics, including mean, median, SD, minimum and maximum, and number and percentage of patients in each category (0, 1, 2, 3, and \geq 4 Gd-enhancing T1 lesions at baseline)

- Normalized brain volume at baseline: summary statistics, including mean, median, SD, minimum, and maximum
- White matter volume at baseline: summary statistics, including mean, median, SD, minimum, and maximum
- Cortical grey matter volume at baseline: summary statistics, including mean, median, SD, minimum, and maximum
- Un-enhancing T1-lesion volume at baseline: summary statistics, including mean, median, SD, minimum, and maximum
- Number of T1 hypo-intense lesions (black holes) at baseline: summary statistics, including mean, median, SD, minimum, and maximum

A listing of MRI assessments at baseline will be provided.

4.4 OUTCOME ANALYSIS

No hypothesis testing will be performed.

For immunology endpoints, pre-immunization levels are those obtained immediately prior to administration of a vaccine.

Patients with missing immunology assessment data will not be included in the calculations. No missing data imputation methods will be applied.

For immunology endpoints, except where stated, tabular presentations will show Group A (Groups A1 and A2 combined) and Group B.

Summaries will be presented for the OC Population only.

4.4.1 Primary Immunology Endpoint

The primary outcome measure is the proportion of patients in Groups A and B with a positive response (IgG) to TT adsorbed vaccine measured 8 weeks after TT booster vaccine administration. Positive response is defined as follows:

- For patients with pre-immunization tetanus antibody titers <0.1 IU/mL, a positive response to the booster TT immunization is defined as an antibody titer ≥ 0.2 IU/mL measured 8 weeks after immunization.
- For patients with pre-immunization tetanus antibody titers ≥ 0.1 IU/mL, a positive response to the booster TT immunization is defined as a 4-fold increase in antibody titers measured 8 weeks after immunization compared with pre-immunization levels.

The number and proportion of patients with a positive response to TT adsorbed vaccine will be presented by treatment group. The difference between treatment groups A and B in positive response rates and the associated 95% CI will also be presented using a normal approximation method.

Levels of anti-tetanus antibody in patients in Groups A and B measured 8 weeks after a booster TT vaccine administration will be summarized descriptively by treatment, showing the following summary statistics:

- Number and percentage of patients with values \leq LLQ
- Number and percentage of patients with values $>$ LLQ
- Geometric mean of known values $>$ LLQ
- 95% CI for geometric mean of known values $>$ LLQ, calculated using a normal approximation method on the log scale and then back-transformed to the original scale
- Geometric mean of all nonmissing values, imputing $LLQ \div 2$ for values \leq LLQ
- 95% CI for geometric mean of all nonmissing values, imputing $LLQ \div 2$ for values \leq LLQ, calculated using a normal approximation method on the log scale and then back-transformed to the original scale
- Median of known values $>$ LLQ
- Median of all nonmissing values, imputing $LLQ \div 2$ for values \leq LLQ

To aid comparison back to pre-vaccination levels, the following pre-vaccination summary statistics will also be included in the tabular summary at 8 weeks:

- Geometric mean of known pre-vaccination values $>$ LLQ
- Geometric mean of all nonmissing pre-vaccination values, imputing $LLQ \div 2$ for values \leq LLQ

4.4.2 Secondary Immunology Endpoints

4.4.2.1 Tetanus Toxoid Adsorbed Vaccine Response Measured 4 weeks after Vaccine Administration

The proportion of patients in Groups A and B with a positive response (IgG) to TT vaccine measured 4 weeks after TT vaccine administration will be compared. Positive response is defined as follows (this differs from the definition of response used for the 8-week assessment above):

- For patients with pre-immunization tetanus antibody titers <0.1 IU/mL, a positive response to the booster TT immunization is defined as an antibody titer ≥ 0.2 IU/mL measured 4 weeks after immunization.
- For patients with pre-immunization tetanus antibody titers ≥ 0.1 IU/mL, a positive response to the booster TT immunization is defined as a 2-fold increase in antibody titers measured 4 weeks after immunization compared with pre-immunization levels.

The number and proportion of patients with a positive response to TT adsorbed vaccine will be presented by treatment group. The difference between treatment groups A and B in positive response rates and the associated 95% CI will also be presented using a normal approximation method.

Levels of anti-tetanus antibody in patients in Groups A and B measured 4 weeks after a booster vaccine will be summarized descriptively by treatment group using the same summary statistics as presented above for the primary immunology endpoint at 8 weeks after vaccine administration.

4.4.2.2 23-Valent Pneumococcal Polysaccharide Vaccine and Pneumococcal Conjugate Booster

The 23-PPV vaccine is assessed by measurement of 23 anti-pneumococcal antibody serotypes (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F). The 13-PCV vaccine acts as a booster to the 23-PPV vaccine, and the 13-PCV vaccine is assessed by measurement of 13 anti-pneumococcal antibody serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F). At the time this SAP was prepared, it is known that no data can be reported for Serotype 6A. Therefore only 12 of the planned 13 serotypes can be analysed for the 13-PCV booster, and all of these 12 serotypes are included in the 23 serotypes which make up the 23-PPV assessments.

Group A1: Patients in Group A1 receive the 23-PPV vaccine at Week 16 and also the 13-PCV booster vaccination 4 weeks later at Week 20. All 23 serotypes are assessed immediately prior to 23-PPV vaccination at Week 16, again prior to the 13-PCV “booster” 4 weeks later at Week 20, and then again 4 weeks after that at Week 24.

Group A2: Patients in Group A2 receive the 23-PPV vaccine at Week 16, but do not receive the 13-PCV “booster”. All 23 serotypes are assessed immediately prior to 23-PPV vaccination at Week 16, again 4 weeks later at Week 20 and again 4 weeks after that at Week 24.

Group B: Patients in Group B follow a similar schedule to Group A2, but earlier in the study. They receive the 23-PPV vaccine at Week 4, and do not receive the 13-PCV “booster”. All 23 serotypes are assessed immediately prior to 23-PPV vaccination at Week 4, again 4 weeks later at Week 8 and again 4 weeks after that at Week 12.

Summaries will show the following groups separately: Group A1, Group A2, Group A (Groups A1 and A2 combined), and Group B. Pairwise between-group comparisons will show:

- Group A1 versus Group A2
- Group A1 versus Group B
- Group A2 versus Group B
- Group A (A1 and A2 combined) versus Group B

Note that the first 3 of the 4 comparisons above, which involve treatment groups A1 and A2 separately, should be interpreted with some caution, since patients were not assigned to these 2 treatment groups randomly (patients were randomized to Group A or

Group B, and within Group A were non-randomly assigned to Group A1 or A2, based on seasonality considerations).

A positive response against a serotype is defined as developing either a 2-fold increase in level or a > 1 $\mu\text{g/mL}$ rise in level, compared with pre-immunization levels.

At 4 weeks after the 23-PPV vaccine, the number and proportion of patients in Groups A1, A2, A (A1 and A2 combined), and B with a positive response (as defined above) against each of the 23 serotypes will be presented. For the same 4 pairwise between-group comparisons described earlier in this section, pairwise between-group differences in positive response rates and the associated 95% CI will also be presented for each serotype, using a normal approximation method.

At 4 weeks after the 23-PPV vaccine, the number and proportion of patients in Groups A1, A2, A (A1 and A2 combined), and B with positive responses (as defined above) against at least 2 of the 23 serotypes will also be presented. For the same 4 pairwise between-group comparisons described earlier in this section, pairwise between-group differences in response rates and the associated 95% CI will also be presented, using a normal approximation method.

At 4 weeks after the 23-PPV vaccine, the number and proportion of patients in Groups A1, A2, A (A1 and A2 combined), and B with positive responses (as defined above) against at least 50% of the serotypes (≥ 12 of 23) will also be presented. For the same 4 pairwise between-group comparisons described earlier in this section, pairwise between-group differences in response rates and the associated 95% CI will also be presented, using a normal approximation method.

At 8 weeks after the 23-PPV vaccine (which is 4 weeks after Group A1 patients received the 13-PCV booster), the number and proportion of patients in Groups A1, A2, A (A1 and A2 combined), and B with a positive response (as defined above) against each of the 23 serotypes will be presented. For the same 4 pairwise between-group comparisons described earlier in this section, pairwise between-group differences in positive response rates and the associated 95% CI will also be presented for each serotype, using a normal approximation method.

Levels of anti-pneumococcal antibodies ($\mu\text{g/mL}$) against each of the 23 different serotypes in patients in Groups A1, A2, A (A1 and A2 combined), and B measured 4 weeks and 8 weeks after administration of 23-PPV (which is 4 weeks after Group A1 patients received the 13-PCV booster) will be summarized descriptively by group using the same summary statistics as presented in Section 4.4.1 for the primary immunology endpoint.

4.4.2.3 Keyhole Limpet Hemocyanin

Levels of anti-KLH antibody IgG in patients in Groups A and B measured at 4, 8, and 12 weeks after first KLH administration will be summarized descriptively by treatment group using the same summary statistics as presented in Section 4.4.1 for the primary immunology endpoint.

Levels of anti-KLH antibody IgM in patients in Groups A and B measured over time at 4, 8, and 12 weeks after first KLH administration will be summarized descriptively by treatment group using the same summary statistics as presented in Section 4.4.1 for the primary immunology endpoint.

4.4.2.4 Influenza Vaccine Response

Between-group comparisons of influenza vaccine response require comparison of Groups A2 and B. As noted above in Section 4.4.2.2, comparisons between Groups A2 and B should be interpreted with some caution, since patients were not assigned to Group A2 randomly (patients were randomized to Group A or B, and within Group A were non-randomly assigned to Group A1 or A2, based on seasonality considerations).

The number and percentage of patients in Groups A2 and B who achieve seroprotection, defined as specific HI titers >40 at 4 weeks after vaccination, will be presented by treatment group. The difference between Groups A2 and B in seroprotection rates, and the associated 95% CI will also be presented using a normal approximation method.

The number and percentage of patients in Groups A2 and B who achieve a 2-fold increase in specific HI titers at 4 weeks after vaccination will be presented by treatment group. The difference between Groups A2 and B in the proportion of patients achieving a 2-fold increase, and the associated 95% CI will also be presented using a normal approximation method.

The number and percentage of patients in Groups A2 and B who achieve a 4-fold increase in specific HI titers at 4 weeks after vaccination will be presented by treatment group. The difference between Groups A2 and B in the proportion of patients achieving a 4-fold increase, and the associated 95% CI will also be presented using a normal approximation method.

The number and percentage of patients in Groups A2 and B who achieve seroconversion at 4 weeks after vaccination, defined as a pre-vaccination antibody titer <10 and a HI titer >40 at 4 weeks after vaccination, will be presented by treatment group. The difference between Groups A2 and B in seroconversion rates, and the associated 95% CI will also be presented using a normal approximation method.

Strain-specific GMTs in patients in Groups A2 and B measured 4 weeks after vaccination will be summarized descriptively by treatment group using the same summary statistics as presented in Section 4.4.1 for the primary immunology endpoint.

Strain-specific GMT ratio (post-vaccination:pre-vaccination) in patients in Groups A2 and B will be summarized descriptively by treatment group; summary statistics calculated will include mean, median, SD, minimum, and maximum.

4.4.3 Other Secondary Endpoints (Magnetic Resonance Imaging)

After baseline, MRI assessments are taken at Years 1, 2, 3, 4, and 5 and at early termination. As the ISP is the main focus for this primary analysis, postbaseline MRI assessments will be presented only in a data listing and not summarized or analyzed at this stage. These postbaseline MRI assessments may be summarized or analyzed in a future analysis when more mature OOE data are available. The postbaseline MRI assessments are as follows:

- T2 lesion volume
- Number of new and/or enlarging T2 lesions since previous MRI
- Number of Gd-enhancing lesions
- Change from baseline in percent brain volume
- Change from baseline in cortical grey matter volume
- Change from baseline in white matter volume
- Unenhancing T1 lesion volume
- Number of Gd-enhancing lesions evolving to black holes since previous MRI
- Number of new T1 hypo-intense (unenhancing) lesions since previous MRI

4.4.4 Exploratory Immunology Endpoints

Between-group comparisons of the exploratory immunology endpoints described below require comparison of Groups A1 and A2, A1 and B, A1 and A2, and A and B. As noted in Section 4.4.2.2 above, the first three of these four comparisons should be interpreted with some caution, since patients were not assigned to Groups A1 and A2 randomly (patients were randomized to Group A or Group B, and within Group A were non-randomly assigned to Group A1 or A2, based on seasonality considerations).

4.4.4.1 Overall Antibody Response to 23-PPV Vaccine

The following analyses will be considered exploratory and may be undertaken, depending on data availability at the time of the primary analysis.

Levels of overall antibody response to the 23-PPV vaccine, IgG (using ELISA) and IgM (using ELISA), measured 4 weeks after administration of the 23-PPV vaccine, and 8 weeks after administration of the 23-PPV vaccine (which is 4 weeks after Group A1 patients received the 13-PCV booster) for patients in Groups A1, A2, A (A1 and A2 combined) and B will be summarized descriptively by treatment group using the same summary statistics as presented in Section 4.4.1 for the primary immunology endpoint.

4.4.4.2 Overall Antibody Response to 13-PCV Vaccine

The following analyses will be considered exploratory and may be undertaken, depending on data availability at the time of the primary analysis.

Levels of overall antibody response to the 13-PCV vaccine, IgG (using ELISA) and IgM (using ELISA), measured 8 weeks after administration of the 23-PPV vaccine (which is 4 weeks after Group A1 patients received the 13-PCV booster) for patients in Groups A1, A2, A (A1 and A2 combined), and B will be summarized descriptively by treatment group using the same summary statistics as presented in Section 4.4.1 for the primary immunology endpoint.

4.4.5 Sensitivity Analyses

If there are any reported major protocol deviations relating to, or other issues reported which may affect data quality or analysis interpretability for a specific primary or secondary immunology endpoint, then as sensitivity analyses, the summaries and analyses specified above for that specific endpoint may be repeated excluding those patients with major protocol deviations/other issues.

4.4.6 Subgroup Analyses

No subgroup analysis is currently planned but may be performed if deemed necessary.

4.5 IMMUNOPHENOTYPING ANALYSES

For immunophenotyping analyses, data will be presented for Groups A1 and A2 separately as well as for Group A (Groups A1 and A2 combined) and Group B.

Summaries will be presented separately within the following study periods:

- ISP
- SFU Period after the ISP (these patients did not enter the OOE)
- OOE
- SFU Period after completing the OOE

The humoral and cellular immunity outcome measures in this study are as follows:

- Flow cytometry, which will include (but is not limited to) the following cells:
 - Total B cells (CD19+)
 - B-cell subsets (e.g., memory B cells, naïve B cells, and plasma cells)
 - Total T cells (CD3+)
 - T helper cells (CD3+ and CD4+)
 - Cytotoxic lymphocyte T (CD3+ and CD8+)
 - Natural killer cells (CD3– and CD16/56+)
- Quantitative Ig:lg levels (including total Ig, IgG, IgG subtypes, IgM, and IgA)

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22/Statistical Analysis Plan BN29739

For each flow cytometry parameters, the absolute values and change from baseline (Day 1) will be summarized over time by treatment group. Summary statistics calculated will include mean, median, SD, minimum, and maximum. For CD19 cells, the number and percentage of patients whose CD19 counts have repleted will be presented at each timepoint. Repletion is defined as the CD19-cell count having returned to their baseline value (Day 1) or lower limit of normal (≥ 80 cells/ μL), whichever is lowest. The median CD19-cell count will be displayed graphically over time from the start of study treatment.

For immunoglobulin levels (IgG, IgM, and total Ig), the absolute values and change from baseline will be summarized over time by treatment group. Summary statistics calculated will include mean, median, SD, minimum, and maximum. At each timepoint, the number and percentage of patients with immunoglobulin levels lower than the lower limit of normal will be presented. For each immunoglobulin, the number and percentage of patients with single and replicated laboratory abnormalities will be summarized by treatment group. The mean immunoglobulin levels (IgG, IgM, and total Ig) will be displayed graphically over time from the start of study treatment.

4.6 SAFETY ANALYSES

For safety analyses, data will be presented for Groups A1 and A2 separately as well as for Group A (Groups A1 and A2 combined) and B.

All summaries of safety data will be based on the Safety Population.

4.6.1 Exposure to Study Medication (Ocrelizumab)

4.6.1.1 Exposure to Ocrelizumab during the ISP

Patients will be considered to have received a dose of ocrelizumab treatment if at least one part of one infusion of that dose (i.e., either Day 1 or 15 for dual infusions) was given.

Treatment duration for ocrelizumab-treated patients in the ISP will be calculated as the date of the last recorded observation during the ISP (the date reported on the ISP Completion/Early Discontinuation electronic Case Report Form [eCRF]) minus the date of first dose of ocrelizumab. If protocol requirements are followed exactly, this duration should be 168 days (24 weeks) for patients who do not withdraw/discontinue early.

Exposure to ocrelizumab for patients in Groups A1, A2, and A (Groups A1 and A2 combined) during the ISP will be summarized as follows:

- Dose received on Day 1: number and percentage of patients who received ocrelizumab dose
- Dose received on Day 15: number and percentage of patients who received ocrelizumab dose

- Total cumulative dose of ocrelizumab (mg; Day 1 + Day 15): summary statistics, including mean, median, SD, minimum, and maximum
- Receiving <80% and ≥80% of the planned infusion on Day 1: number and percentage of such patients
- Receiving <80% and ≥80% of the planned infusion on Day 15: number and percentage of such patients
- Pretreatment with steroids on Day 1: number and percentage of patients pretreated on Day 1
- Pretreatment with steroids on Day 15: number and percentage of patients pretreated on Day 15
- Pretreatment with antihistamines on Day 1: number and percentage of patients pretreated on Day 1
- Pretreatment with antihistamines on Day 15: number and percentage of patients pretreated on Day 15

A listing of information relating to exposure to ocrelizumab will be provided.

4.6.1.2 Exposure to Ocrelizumab during the OOE

Patients will be considered to have received a dose of ocrelizumab treatment if at least one part of one infusion of that dose (i.e., either Day 1 or 15 for dual infusions) was given.

The duration of observation for a patient will be calculated as:

(Date of the day prior to the infusion of the last dose in OOE – date of the first infusion in the dose given during the ISP) + 1

Exposure to ocrelizumab for patients in Groups A1, A2, A (Groups A1 and A2 combined), and B during the OOE will be summarized as follows:

- Treatment duration: number and percentage of patients who received 0–23 weeks of treatment, 24–47 weeks of treatment, 48–71 weeks of treatment, 72–95 weeks of treatment, etc.
- Number of ocrelizumab doses: number and percentage of patients receiving 1, 2, 3, 4, etc. doses and summary statistics for the number of ocrelizumab doses (mean, SD, and median)
- Total cumulative dose of ocrelizumab during OOE (mg): summary statistics, including mean, median, SD, minimum, and maximum

A listing showing duration of exposure to ocrelizumab during the ISP and OOE will be provided.

4.6.2 Adverse Events

Adverse events will be summarized for the ISP and the OOE. Adverse events reported during the SFU Period or B-cell Monitoring Period will be included in the period of previous dose received.

Safety data from this trial will also be included in pooled safety analyses of MS patients treated with ocrelizumab (e.g., malignancy) at interim analyses. These analyses are not described in this document.

4.6.2.1 Adverse Events during the ISP

Adverse events will be defined as all adverse events, except non-serious MS relapses, but including infusion-related reactions (IRRs) and serious MS relapses. Therefore, those adverse events recorded on the “adverse event” and “infusion-related reaction (IRR)” CRF pages will be included.

For each adverse event recorded, the term entered by the investigator describing the event (the “reported term”) will be assigned a standardized term (the “preferred term”) based on the MedDRA WHO dictionary of terms. All analyses of adverse event data will be performed using the PTs unless otherwise specified.

All adverse events will be mapped to PTs and superclass terms and included in a data listing (a separate listing showing relapse information will also be presented). For all summary tables, the adverse events will be sorted by SOC (in decreasing order of overall incidence) and then by PT (in decreasing order of overall incidence). An adverse event profile summary table will be presented to provide an overview of adverse events reported in the ISP. Additionally, the most frequent adverse events ($\geq 5\%$ in any treatment group) will be presented by PT.

Summaries of adverse events will be generated by summarizing the incidence of treatment-emergent adverse events only. Treatment-emergent events are defined as those adverse events with observed or imputed onset date on or after the start date of study treatment (ocrelizumab or any vaccinations). Only where the most extreme intensity is greater than the initial intensity will events with an onset date prior to the start of study treatment (and with an end date on or after the start of study treatment) be considered treatment-emergent. An adverse event with a completely missing, non-imputed start date will be assumed to be treatment-emergent unless the adverse event has a complete non-imputed end date that is prior to start of study treatment.

Adverse events will be assigned to a dose if the adverse event onset date is on or after the date of the first infusion of that dose but before the first infusion of the next treatment dose. Adverse events that start prior to the first dose and worsen during treatment (i.e., treatment-emergent) will be assigned to the first treatment dose.

For each treatment group, the incidence count for each adverse event PT will be defined as the number of patients reporting at least 1 treatment-emergent occurrence of the event. The incidence rate will be calculated as the incidence count divided by the total number of patients in the population. Each table will also present the overall number of patients experiencing at least 1 adverse event and the total number of adverse events reported (multiple occurrences of the same adverse event in one patient will be counted only once at the most extreme intensity). For adverse events leading to death, the most extreme intensity will be overwritten by Grade 5 (death).

Serious adverse events will be defined as all serious adverse events, which includes serious MS relapses and serious IRRs. Serious adverse events will be summarized for each treatment group by SOC and PT, and presented in a data listing. Additionally, the most frequent serious adverse events ($\geq 1\%$) will be presented by PT for each treatment group. A separate listing with relapses considered as serious adverse events will be presented. Related adverse events and serious adverse events will be summarized by SOC and PT for each treatment group and separately for adverse events related to (or suspected to be related to) treatment with each of the following:

- Ocrelizumab
- Methylprednisolone
- KLH
- Tetanus and diphtheria vaccine
- Tetanus, diphtheria, and pertussis vaccine
- 23-PPV
- 13-PCV
- Influenza vaccine

Concomitant treatments for adverse events (excluding IRRs and MS relapses) will be summarized by class and PT. Also concomitant treatments starting during the ISP or during the SFU Period following the ISP will be summarized by class and PT.

Adverse events and serious adverse events will be summarized by intensity (most extreme intensity) and overall, by SOC and PT. Additionally, adverse events of intensity grades 3, 4, or 5 (most extreme intensity) will be summarized by intensity and overall, by SOC and PT.

All patient deaths during the study (all study periods) will be included in a data listing.

A patient may experience an adverse event that leads to the discontinuation of their study treatment. Discontinuation of study treatment for an adverse event may not necessarily lead to discontinuation from the study because patients can enter the SFU Periods. Only adverse events that led to the discontinuation of study treatment are of interest. Patients who withdraw early from the study because of adverse events will be

Ocrelizumab—F. Hoffmann-La Roche Ltd
26/Statistical Analysis Plan BN29739

Clinical Study Report: ocrelizumab - F. Hoffmann-La Roche Ltd
Protocol BN29739 Report Number 1079337

summarized under disposition. The number of patients who experienced an adverse event that led to discontinuation of study treatment will be summarized by SOC and PT for each treatment group. A listing will be presented showing all adverse events which led to discontinuation of study treatment.

The number of patients who experienced an adverse event that led to modification or interruption of study drug will be summarized by SOC and PT for each treatment group.

A glossary of superclass terms, PTs and verbatim terms for adverse events will be provided. Also a glossary of superclass terms and PTs for adverse events baskets will be provided.

To comply with the reporting requirements of www.clinicaltrials.gov, the following two tabular summaries will be provided for the ISP. For the two summaries below, unlike all other adverse event summaries in this study, multiple occurrences of the same adverse event in an individual are counted separately:

- Non-serious adverse events reported in $\geq 5\%$ of patients in any treatment group will be summarized by SOC and PT. Non-serious relapses will be excluded here. Within each treatment group, the number and percentage of patients reporting such adverse events, and the number and percentage of events reported, will be presented.
- Serious adverse events will be summarized by SOC and PT. Within each treatment group, the number and percentage of patients reporting serious adverse events, and the number and percentage of serious adverse events reported, will be presented. Further, the total number of serious adverse events in each treatment group that were treatment-related, fatal, and treatment-related and fatal will be presented.

4.6.2.2 Adverse Events during the OOE

Adverse events during the OOE will be handled and reported using the same general approaches as described above for the ISP.

An adverse event profile summary table will be presented to provide an overview of adverse events reported in the OOE. Adverse events and serious adverse events will be summarized by SOC and PT also.

Concomitant treatments for adverse events will be summarized by class and PT. Also concomitant treatments starting during the OOE or during the SFU Period following the OOE will be summarized by class and PT.

The number of patients who experienced an adverse event within the OOE that led to interruption of study drug will be summarized by SOC and PT for each treatment group.

4.6.2.3 Adverse Events, All Study Periods

When presenting adverse events across all study periods, the same general approaches to handling and reporting adverse events will be applied, as described above for the ISP.

Ocrelizumab—F. Hoffmann-La Roche Ltd
27/Statistical Analysis Plan BN29739

An adverse event profile summary table will be presented to provide an overview of adverse events reported in the OOE. Adverse events and serious adverse events will be summarized by SOC and PT also.

Concomitant treatments for adverse events (excluding IRRs and MS relapses) will be summarized by class and PT.

Concomitant procedures/surgeries will be summarized by class and PT.

4.6.3 Selected Adverse Events

4.6.3.1 Progressive Multifocal Leukoencephalopathy

PML will be categorized as a serious adverse event per guidance on the diagnosis of PML in protocol. Patients with PML, if any, will be included in the listing of serious adverse events.

4.6.3.2 Infections and Serious Infections

Infections will be defined from the adverse event data using the MedDRA SOC of “Infections and Infestations”. An infection will be defined as serious if the event is a serious adverse event.

A listing of infections (defined using the MedDRA SOC “Infections and Infestations”) with pathogen information code will be provided. An additional listing will display adverse events from other SOCs with the pathogen information code. Also a listing will display non-serious infections treated with an intravenous anti-infective.

Immunization Study Period

Infections and serious infections will be summarized by SOC and PT. Infections by intensity will be summarized also. If a patient has multiple events, the most extreme intensity will be taken. Infections and serious infections will also be summarized by pathogen type. The number of infections and serious infections per 100 patient-years will be calculated and summarized.

Optional Ocrelizumab Extension

The same summaries will be presented for OOE as for ISP, with the exception of summaries of infections and serious infections by pathogen type.

All Periods

The same summaries will be presented for all study periods as for ISP.

4.6.3.3 Infusion-Related Reactions

An IRR and its corresponding symptoms are collected on the dedicated eCRF.

The symptom(s) of an IRR and the IRR itself may be of different intensities. As other symptoms can be recorded as free-text on the eCRF page, symptoms will be coded in

MedDRA and summarized by PTs. IRRs are categorized by the time of the event occurring during the infusion and within 24 hours of completion of the infusion.

A listing of patients with at least one IRR will be presented, including associated symptoms. This listing will be repeated to show the subset of patients with at least one IRR/symptom at Grade 3 or above (intensity).

Immunization Study Period

During the ISP, pretreatments will be summarized by infusion and overall, by class and PT (multiple occurrences of the same treatment in one individual are counted once per infusion).

By infusion and overall during the ISP, the number and percentage of patients with at least one IRR will be presented (patients with multiple events within an infusion will count only once). In addition, the total number of patients with IRR symptoms will be summarized by infusion and overall (multiple occurrences of an IRR symptom in one patient at one infusion (or overall) are counted once for that infusion (or overall)). The total number of IRR symptoms will also be summarized by infusion and overall. IRR symptoms will be summarized by SOC and PT.

During the ISP, the number and percentage of patients with IRRs and the total number of IRRs will be summarized by intensity and overall, and by infusion. For patients who have multiple IRRs, the most extreme intensity will be taken.

By infusion and overall during the ISP, the number and percentage of patients with at least one serious IRR will be presented (patients with multiple events within an infusion will count only once). In addition, the total number of patients with IRR symptoms resulting from serious IRRs will be summarized by infusion and overall (multiple occurrences of a serious IRR symptom in one patient at one infusion (or overall) are counted once for that infusion (or overall)). The total number of IRR symptoms resulting from serious IRRs will also be summarized by infusion and overall. Serious IRR symptoms will be summarized by SOC and PT.

By infusion and overall during the ISP, the number and percentage of patients with at least one IRR, the total number of IRRs, and the number of IRRs will be summarized by the time of events (during infusion, within 24 hours after end of infusion). Multiple occurrences of an IRR in one patient within one time period are counted once.

During the ISP, the number and percentage of patients reporting adverse events on the day or the day after an infusion, and the total number of such events will be presented, and these adverse events will be summarized by SOC and PT.

During the ISP, the number and percentage of patients receiving concomitant treatments for IRRs and the total number of such treatments will be presented, and these

concomitant treatments will be summarized by class and PT (multiple occurrences of the same treatment in one individual are counted once).

IRRs, serious IRRs and symptoms at Day 1, Dose 1 will be summarized separately for the 2 different ocrelizumab formulations used in this study (v0.4 and v1.0).

Optional Ocrelizumab Extension

By infusion and overall during the OOE, the number and percentage of patients with at least one IRR will be presented (patients with multiple events within an infusion will count only once). In addition, the total number of patients with IRR symptoms will be summarized by infusion and overall (multiple occurrences of an IRR symptom in one patient at one infusion (or overall) are counted once for that infusion (or overall)). The total number of IRR symptoms will also be summarized by infusion and overall. IRR symptoms will be summarized by SOC and PT.

During the OOE, the number and percentage of patients with IRRs and the total number of IRRs will be summarized by intensity and overall, and by infusion. For patients who have multiple IRRs, the most extreme intensity will be taken.

By infusion and overall during the OOE, the number and percentage of patients with at least one serious IRR will be presented (patients with multiple events within an infusion will count only once). In addition, the total number of patients with IRR symptoms resulting from serious IRRs will be summarized by infusion and overall (multiple occurrences of a serious IRR symptom in one patient at one infusion (or overall) are counted once for that infusion (or overall)). The total number of IRR symptoms resulting from serious IRRs will also be summarized by infusion and overall. Serious IRR symptoms will be summarized by SOC and PT.

4.6.3.4 Malignancies and Premalignant Lesions

Malignancies and premalignant lesions will be listed.

4.6.4 Laboratory Data

4.6.4.1 General Laboratory Evaluation

The summaries described below for general laboratory assessments will be produced for both the ISP and for the OOE separately.

For each laboratory test, absolute and changes from baseline values at each visit will be summarized by treatment group. Summary statistics calculated will include mean, median, SD, minimum, and maximum. The baseline value will be the last value prior to the first dose of ocrelizumab for patients in Group A and prior to the first immunization for patients in Group B. When laboratory data are presented over time, the laboratory values will be time-windowed into a common visit structure. If multiple values of the same laboratory parameter occur within the same time window, the worst value (i.e., the

value furthest away from the midpoint of the normal range) will be included in calculations of summary statistics.

For each laboratory test, the number and percentage of patients with single and replicated laboratory abnormalities will be summarized by treatment group.

In addition, for liver laboratory parameters, the number and percentage of patients with an elevated postbaseline AST or ALT levels will be summarized by treatment group.

During the SFU Period after either the ISP or the OOE, for each laboratory test, absolute and changes from baseline values at each visit will be summarized by treatment group. Summary statistics calculated will include mean, median, SD, minimum, and maximum. These summaries will only be presented if there is a sufficient volume of patient data available to allow meaningful interpretation.

Section 6.5.2 of the protocol states that for each laboratory test, individual patient values will be listed, and values outside the standard reference range will be flagged. To maintain consistency with the other Phase 3 studies in the ocrelizumab program, this data listing will not be prepared. The summary tables described above are considered adequate to describe general laboratory abnormalities, without the need for this data listing.

4.6.4.2 Anti-Drug Antibodies

The summaries described below for ADAs will be produced for both the ISP and for the OOE separately.

ADAs will be summarized descriptively. The baseline prevalence and postbaseline incidence of ADAs will be displayed. The number of patients with treatment-induced ADAs and the number of patients with treatment-enhanced ADAs will also be displayed.

A table will be presented that summarizes ocrelizumab serum concentrations ($\mu\text{g/mL}$) at timepoints when ADA samples were collected and analyzed (summary statistics: mean, median, SD, minimum, maximum, coefficient of variation [percentage], geometric mean, number, and percentage of samples with concentration $\leq 20 \mu\text{g/mL}$).

A listing by treatment group covering both ISP and OOE showing anti-ocrelizumab antibody data will be presented for patients with at least one ADA-sampled datum.

4.6.5 Vital Signs and Electrocardiogram

The summaries for vital sign parameters and ECG results will be presented separately within the ISP and OOE study periods.

The following vital signs parameters will be assessed:

- Systolic blood pressure

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31/Statistical Analysis Plan BN29739

- Diastolic blood pressure
- Pulse rate
- Respiratory rate
- Temperature
- Weight

For each vital signs parameter within each study period (ISP and OOE), absolute and change from baseline values will be summarized by treatment group at study visits that do not include an ocrelizumab infusion. For each vital signs parameter within each study period (ISP and OOE), absolute values and the value of the change from the pre-infusion baseline at that visit will be summarized by treatment group at each study visit that includes an ocrelizumab infusion (summary statistics: mean, median, SD, minimum, and maximum). At each visit at which vital signs parameters are assessed, summary statistics calculated will include mean, median, SD, minimum, and maximum. All vital signs data will be presented in a data listing by treatment group and covering all study periods.

ECG results will be summarized by treatment group within each study period (ISP and OOE) and will show the number and percentage of patients with normal, abnormal (not clinically significant), and abnormal (clinically significant) findings at baseline cross-tabulated with postbaseline ECG results in a shift table format. All ECG results will be presented in a data listing by treatment group and covering all study periods.

4.6.6 Pregnancies

For any pregnancies that occur during the study, pregnancy information will be presented in a data listing.

4.7 MISSING DATA

Missing data will not be imputed.

4.8 INTERIM ANALYSES

No interim analysis of immunology endpoints is planned.

Analyses of malignancies and other safety analyses of all patients who received at least one dose of ocrelizumab may be done as part of pooled MS ocrelizumab analyses (including other clinical trials data). These analyses are not described in this document. Interim PK analyses may also be performed during the study (not described here but in a separate document).